REMARKS

Claims 1, 17, and 57 have been amended to reflect that formation of the aggregates will be at least 95% complete 10 minutes after mixing. The amendment is supported by the specification (page 5, lines 27-29; page 5, lines 20-24) and claim 14.

Claims 17, 18, 42, 43, 57, and 58 have been amended to reflect the particle size of the claimed invention. The amendment to claim 17 is supported by claim 18. The amendment to claims 42 and 57 is supported by claim 58. The amendment to claims 18, 43, and 58 is supported by the specification (see page 8, first full paragraph; page 23, first paragraph). Claims 50, 51, 54-56, 60-63, 66-68, and 70-71 have been amended to correct dependency. No new matter has been added. Upon entry of this amendment, claims 1-5, 17-22, and 42-71 are active and present in the application.

Request for Reconsideration

Applicants would like to thank Examiner Pande for the courteous and helpful discussion held on October 1, 2007 with Applicants' representative. During this discussion, unexpected and superior properties of the claimed invention were discussed, as well as how such data should be presented.

Nucleic acid enzyme-base sensors have been used for the specific and sensitive detection of cofactors and effectors in the analysis of samples (see, for example, U.S. Pats. Nos. 6,706,474; 6,890,719; U.S. Applications Ser. Nos. 10/144,679; and 10/384,497).

Figure 1 of the present application illustrates one such sensor specific for Pb^{2+}. Enzyme strand 17E (Figure 1a) has been optimized for high activity in the presence of Pb^{2+}. Therefore, the presence of Pb^{2+} can activate the enzyme. In a nucleic acid enzyme-based sensor, this promotes cleavage of the substrate strand 17DS at the single ribo-adenosine position (Figure 1b).

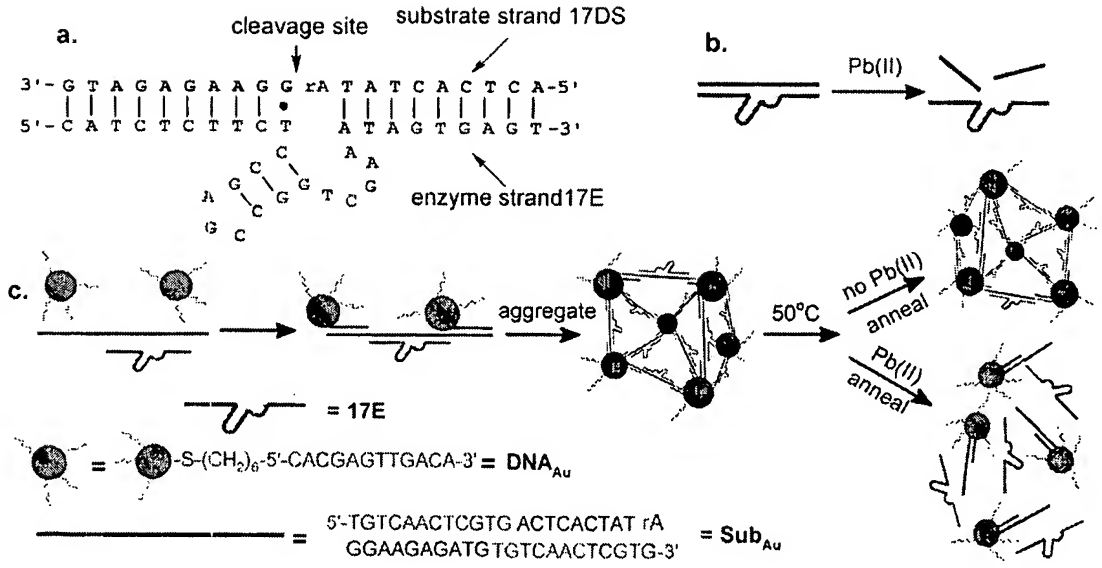


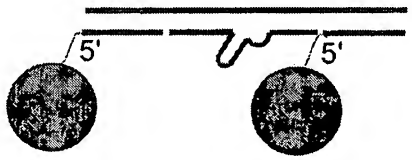
Figure 1

Shown in Figure 1c are two DNA-functionalized 13 nm diameter gold particles, hybridized to both ends of the substrate. The substrate strands (both free substrate and substrate hybridized with the enzyme strand) can act as linkers for the DNA-functionalized gold particles to form aggregates, which have a blue color. In the presence of Pb^{2+}, the substrates are cleaved. The cleaved substrates no longer act as linkers for the particles and the color becomes red.

Unfortunately, though highly sensitive and selective, this type of analytical sensor requires heating to above 50 °C for several minutes and cooling slowly to room temperature in 2 hours for detection. The present invention does away with this requirement for heating, allowing these sensors to be used not only in laboratories, but by consumers in their homes, or by technicians in the field. The invention is based on the surprising results that were obtained by, *inter alia*: (1) altering the alignment of the particles from head-to-tail to tail-to-tail; (2) using larger particles.

The first discovery is that aggregation of particles is influenced by their alignment with respect to each other. Particles may be aligned in two ways, "head-to-tail" or "tail-to-tail" (Figure 3 of the application).

A. Head-to-Tail arrangement of gold nanoparticles



B. Tail-to-Tail arrangement of gold nanoparticles

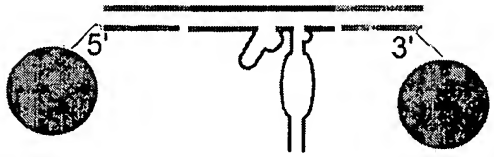


Figure 3

In previous sensors the particles are aligned in the "head-to-tail" fashion (Figure 3A). If the particles are aligned in the "head-to-tail" manner, only one kind of thiol-modified DNA is needed to attach the DNA to the particle. In this configuration, it is difficult for the particles to aggregate, possibly due to steric effects. Heating and cooling is thus necessary to promote the assembly of particles. However, it has now been discovered that when a "tail-to-tail" (Figure 3B) alignment is used, the particles can aggregate at ambient temperature.

Independent claims 1 and 57 embody this "tail-to-tail" arrangement. Since both 3' - and 5' -thiol-modified polynucleotides are needed to produce "tail-to-tail" aligned particles, both types of nucleotides are included in the claims.

The second discovery is that the color of particle aggregates is mainly governed by the size of the aggregates. Thus, the rate of aggregation being equal, the rate of color change increases using larger particles. Accordingly, as compared to previous sensors with 13 nm diameter particles, when a mixture of 13 and 35 nm diameter particles is used, the rate of color change is faster. The rate of color change further increases if only particles of 35 nm diameter are used. Such improvements are illustrated by Figure 4 of the application and embodied by independent claims 17 and 57 as presently amendment.

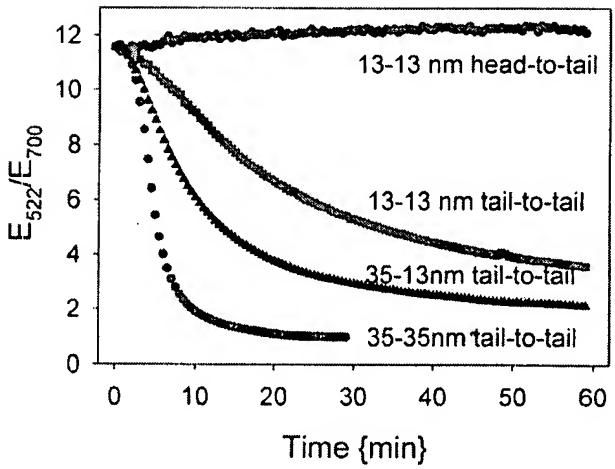


Figure 4

Claims 1-5, 17-22, 42-71 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Cuenoud and Szostak (Nature, vol. 375, pp. 611-614, 1995) in view of Mirkin et al. (U.S. Pat. No. 6,361,944, issued March 26, 2002); Frauendorf and Jaeschke (Bioorganic and Medicinal Chemistry, 9: 2521-2524, 2000) and further in view of Joyce and Breaker (WO 98/49346, 1998) and Li and Lu (J. Am. Chem. Soc., vol. 122, no. 42, pp. 10466-10467, 2000). The rejection is respectfully traversed. The cited references, either alone or combination, neither disclose nor reasonably suggest the surprising and unexpected results of the present invention.

As set forth above, the claims as presently amended are drawn to improved sensors that include particles with a "tail-to-tail" arrangement and/or an average diameter of at least 30 nm. Having these features, the sensors have no requirement for heating, allowing for use not only in laboratories, but by consumers in their homes, or by technicians in the field. Moreover, the data demonstrate these improvements are commensurate in scope with the claims as amended, since the claims require the tail-to-tail arrangement and/or the particle size that yield such improved results.

Cuenoud and Szostak are silent as regards the use of particles. Mirkin et al. do not recognize how assays can be improved by the use of a "tail-to-tail" alignment, or by the use

of particles having a larger size. Furthermore, Frauendorf and Jaeschke, Joyce and Breaker, and Li and Lu, are all silent regarding particles and their use in assays. Accordingly, Applicants submit that the unexpected and surprising results obtained demonstrate the unobviousness of the claimed invention. A declaration under 37 CFR § 1.132 describing these results will be filed when available.

Applicants submit that the application is in condition for allowance. Early notice of such action is earnestly solicited.

Respectfully submitted,

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